NIEHS News

Breast Cancer Gene Isolated

A team of researchers at the NIEHS, in collaboration with researchers at the University of Utah Medical Center, have isolated *BRCA1*, a gene that plays a major role in inherited breast cancer and ovarian cancer.

Scientists believe that *BRCA1* is a tumor-suppressor gene, a gene that prevents uncontrolled cell proliferation. Thus, when the gene is inactivated through loss or mutation, cancer can occur.

It has been known for years that the mutant form of *BRCA1*, which is located on human chromosome 17, predisposes women to breast and ovarian cancers. However, the NIEHS and University of Utah researchers are the first to pinpoint the exact location of *BRCA1* and clone it in the laboratory. Using a technique known as positional cloning, the researchers created a detailed map of 17q, the area of the chromosome that contains the breast cancer gene. They then focused on genes in that area expressed in normal breast tissue and compared them with mutational damage in tissue from women known to carry the defective form of *BRCA1*.

Five percent of breast cancer cases are due to inherited susceptibilities including *BRCA1*. Studies of families with defective *BRCA1* genes suggest that more that half the women who carry the gene will be diagnosed with breast cancer by age 50, and 85% will be diagnosed by age 70. Although men in predisposed families also carry the mutant gene, their risk of breast cancer is not significantly increased. Now that the gene has been isolated, studies of the effects of specific mutations will be possible. Kenneth Olden, director of the NIEHS, said, "This represents a landmark discovery with exciting implications for the development of a test to identify women who are at high risk for breast cancer caused by the *BRCA1* gene. However, a great deal of research remains to be done before this discovery will have practical application."

Most women have no family history of breast cancer. It has been thought that "sporadic" breast cancers may involve somatic mutations of *BRCA1*, mutations that cannot be passed to offspring. However, in examining cancerous tissue from 44 patients without a family history of breast or ovarian cancer, the researchers found *BRCA1* mutations in 4 cases. The mutations occurred in all body cells, suggesting that the defective *BRCA1* gene was in fact inherited in the same manner as in families with a history of breast cancer.

Because everyone has two copies of each gene, a child has only a 50% chance of inheriting a defective *BRCA1* gene. For *BRCA1* to cause cancer in a breast cell, both copies of the gene must be lost or damaged. Women born with *BRCA1* mutations have one bad copy of the gene, so only one damaging mutation in a breast cell must occur to lead to cancer: they are one step closer to cancer than women without the damaged gene.

BRCA1 is not the only gene involved in familial breast cancer. *BRCA2*, which has recently been mapped to chromosome 13, has not yet been isolated. However, *BRCA2*, unlike *BRCA1*, is not implicated in ovarian cancer.

An increased risk for breast cancer has also been observed in families with Li-Fraumeni syndrome, which is linked to mutations in the p53 tumor-suppressor gene; ataxia-telangiectasia, linked to the *AT* gene, and congenital retinoblastoma, linked to the *RB1* gene.

Although the isolation of *BRCA1* has no immediate implications for breast cancer screening and treatment in the general population, it significantly advances the long-term goal of research to mitigate genetic defects. Existing tests for the mutation are used only in individuals from families known to carry the defective gene. Isolation of the gene may lead to development of tests for the gene itself rather than tests based on genetic markers. Such a test would have to be able to identify a variety of mutations spread widely across the gene. Until *BRCA1* is better understood, testing for mutations will be limited to research to learn more about the gene.

The introduction of genetic testing into mainstream medical practice has been a major priority issue for the Ethical, Legal, and Social Implications program of the Human Genome Project. In addition, a task force on genetic testing is being set up by the Department of Health and Human Services to consider these issues. The task force will include consumers, geneticists, government officials, and biotechnologists.

In the meantime, a woman with a family history of breast cancer, especially if the cancers were diagnosed at a young age, should discuss early detection procedures for breast cancer with her doctor.

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Gene team. NIEHS Director Kenneth Olden (left) with senior members of the NIEHS team that identified the breast cancer susceptibility gene (left to right): J. Carl Barrett, Roger W. Wiseman, and Andrew Futreal.

NIEHS Launches Clearinghouse

Where do people go when they have questions about environmental health and related issues? Beginning October 1994, the National Institute of Environmental Health Sciences in Research Triangle Park, NC, will provide a major, national information source and referral point for questions about health and the environment with the establishment of EnviroHealth, an environmental health information clearinghouse, accessible toll-free through 1-800-NIEHS94 (643-4794).

Kenneth Olden, NIEHS director, has given the clearinghouse top priority and